Research Article

PREPARATION AND CHARACTERIZATION OF SPRAY DRIED MICROPARTICLE AND SPRAY CHILLED PARTICLE OF MEFENAMIC ACID BY SPRAY DRYING METHOD

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ABSTRACT

Mefenamic acid, an anti-inflammatory drug, exhibits poor water solubility and flow properties, poor dissolution and poor wetting. Consequently, the aim of this study was to improve the dissolution of Mefenamic acid. Microparticles containing Mefenamic acid were produced by spray drying using isopropyl alcohol and water in the ratio of 40:60 (v/v) as solvent system and spray chilling technology by melting the drug and chilled by atomized with nozzle to enhance dissolution rate. The prepared formulations were evaluated for in vitro dissolution and solubility. The prepared drug particles were characterized by scanning electron microscopy (SEM), differential scanning calorimeter (DSC), X-ray diffraction (XRD) and Fourier transform infrared spectroscopy (FT-IR). Dissolution profile of the spray dried micropartical was compared with chilled spray micropartical, pure sample and recrystallized sample. Spray dried micropartical and chilled spray particles exhibited decreased crystallinity and improved micromeritic properties. The dissolution of the Spray dried micropartical and chilled particles were improved compared with recrystallized and pure sample of mefenamic acid. Consequently, it was believed that spray drying of mefenamic acid is a useful tool to improve dissolution but not in case of chilled spray particles because the dissolution of spray chilled particles not increases significance compare to spray dried microspheres. It may be believe to be degradation of drug or variations in the resonance structure or could be due to minor distortion of bond angles. Hence this spray drying technique can be used for formulation of tablets of mefenamic acid by direct compression with directly compressible tablet excipients.

Keywords: Spray drying, spray chilling, Mefenamic acid, Solubility dissolution, crystallinity.

INTRODUCTION

Formulation and manufacture of solid oral dosage forms, and tablets in particular, have undergone rapid change and development over the last several decades. One of the most revolutionary technologies is that of direct compression. Direct compression is economical, facilitates processing without the need of moisture, heat and involves small number of processing steps. In direct tabletting method, it is necessary to increase flowability and compressibility of the bulk powder in order to retain a steady supply of powder mixture to the tabletting machine and sufficient mechanical strength of the compacted tablets. In addition to increasing efficiency of the manufacturing process it is also important to increase bioavailability of the drug by improving the solubility of the bulk drug powder. Spray dried micropartical is one of such techniques to improve the micromeritic properties and dissolution of drug[1].

Consequently, many hydrophobic drugs show erratic and incomplete absorption from the gastrointestinal tract of animals and humans, which may lead to therapeutic failure. Thus, one of the major challenges to drug development today is poor solubility, as an estimated 40% of all newly developed drugs are poorly soluble or insoluble in water[2-6]. As a result, much research has been conducted into methods of improving drug solubility and dissolution rates to increase the oral bioavailability of hydrophobic drugs. Various techniques such as melt adsorption, supercritical fluid processes, using different composition of solvents to prepared the micropartical to improve the dissolution rate of poorly water soluble drugs and amorphous state to improve their dissolution[1,8,20]. Manipulation of the solid state by decreasing crystallinity of drug substances through formation of solid dispersion is one of the methods used for promoting drug dissolution[6,9]. The solid dispersion technique has often proved to be the most successful in improving the dissolution and bioavailability of poorly water soluble active pharmaceutical ingredients because it is simple, economic, and advantageous technique. The concept of solid dispersion covers a wide range of systems. The enhancement in the dissolution rate is obtained by one or a combination of the following mechanisms: eutectic formation, increased surface area of the drug due to precipitation in the carrier, formation of true solid solution, improved wettability, drug precipitation as a metastable crystalline form or a decrease in substance crystallinity. The type of solid dispersion formed depends on both the carrier-drug combination and the method of manufacture[3,19]. Microwaves irradiation was used recently for the preparation of solvent-free solid dispersions and for enhancement of release of the poorly soluble drug, Spray drying is one such technique of preparing solid dispersion and is widely used as an alternative to milling to reduce particle size. Spray chilling or spray congealing is another form of solid dispersion where the melted mass is atomized into droplets, which quickly solidify in a cool air[7]. The advantage in spray chilling is that no additional manufacturing step is needed

to pulverize the solid dispersion. In pharmacy, spray chilling has been used to prepare sustained-release formulations, to improve stability[14,18] and to mask the unpleasant taste[22]. The technique also has the advantages of being free from organic solvents compared to spray drying. The method has also been used by the food industry, for example, to encapsulate vitamins and minerals[4]. Mefenamic acid was chosen as a poorly water soluble drug. Mefenamic acid N-2-3-xylylanthranilic acid is one of the safest and most potent non-steroidal anti-inflammatory drugs being widely used in the market. The drug used to treat rheumatoid arthritis, osteoarthritis, and mild to moderate pain. It has low aqueous solubility and hence poor dissolution. The present work was conducted to improve the wettability, solubility and hence the dissolution of mefenamic acid using spray drying and spray chilling techniques.

MATERIALS AND METHODS

Materials

Mefenamic acid was obtained as a gift sample from Micro labs, Bangalore, India. Isopropyl alcohol was procured from Merck, Mumbai, India. All chemicals and buffers used were of analytical grade.

Preparation of microparticles

Microparticles prepared by spray drying

Spray dried particles consisted of mefenamic acid was prepared by dissolving the 10 gm drug in the mixture of isopropyl alcohol/water (40:60 (v/v) ratio) solution. The solution was spray dried using Mini Spray Dryer LSD -48; (Jay instrument & systems Pvt. Ltd. Mumbai) at a Feed rate of 12%, an vacuum in the system -65 MM WC, Atomization pressure rate 1 kg/cm^2 , Aspirator level at 35%, inlet temperature at 115 ±2°C and outlet temperature at 45 ±1°C. The formed microparticles were separated using cyclone separator, collected and stored in a desiccator at ambient temperature until ready to be used.

Microparticles prepared by spray chilling

Spray chilled particles were prepared by melting the drug at 235 ±5°C. The melt was kept at 235 ±5°C °C and atomized with a pneumatic nozzle (Mini Spray Dryer LSD -48; Jay instrument & systems Pvt. Ltd. Mumbai). Air kept at 20°C. The inner diameter of the pneumatic nozzle was o.1mm, the capillary length was 5mm and the pressure was 1 Kg/cm^2. The particles were collected using cyclone separator and stored in a desiccator.

Recrytallized microparticals prepared

Changes in crystal lattice, being induced by solvents, can influence the physicochemical properties of the substance. Hence the mechanical, micromeritic and dissolution properties of miroparticals were compared with commercial sample and recrystallized sample. Recrystallization of mefenamic acid was carried out using same solvent composition as was used for spray drying mefenamic acid was dissolved in 40 ml of isopropyl alcohol and 60 ml of water with occasional stirring for 30 min . The crystals of mefenamic acid were collected by filtration and were dried at 45^{0}C.

Evaluation of microparticles

Determination of percentage yield and Drug content

The percentage yield of each formulation was determined according to the total recoverable final weight of microparticles (prepared by spray drying and spray chilling) and the total original weight of mefenamic acid.

Microparticals[7] (50 mg) were triturated with 10 ml of water. Allowed to stand for 10 min with occasional swirling and methanol was added to produce 100 ml. After suitable dilution, samples were measured at 332 nm. Drug content was determined from standard plot.

Differential scanning calorimetry (DSC)

A DSC study was carried out to detect possible polymorphic transition during the crystallization process. DSC measurements were performed on a DSC DuPont 9900, differential scanning calorimeter with a thermal analyzer.

Fourier transform infrared (FTIR) spectroscopy

The FTIR spectral measurements were taken at ambient temperature using a Shimadzu, Model 8033 (USA). Samples were dispersed in KBr powder and the pellets were made by applying 5 ton pressure. FTIR spectra were obtained by powder diffuse reflectance on FTIR spectrophotometer.

X-ray analysis

X-Ray powder diffraction patterns were obtained at room temperature using a Philips X' Pert MPD diffractometer, with Cu as anode material and graphite monochromator, operated at a voltage of 40 mA, 45 kV.The process parameters used were set as scan step size of 0.0170 (2θ).

Scanning electron microscopy (SEM)

Scanning electron microscopic (Joel- LV-5600, USA, with magnification of 250x) photographs were obtained to identify and confirm spherical nature and Surface topography of the crystals.

Micromeritic properties

Particle size of recrystallized sample, pure samples, spay dried microparticals and spray chilling particle were determined by microscopic method using calibrated ocular micrometer. Apparent particle densities of microparticles (prepared by spray drying and spray chilling) were measured using a Pycnometer. Carr's index was determined from powder volumes at the initial stage and after 1250 tappings to constant volume (Electolab, Mumbai). The angle of repose of microparticles (prepared by spray drying and spray chilling) and commercial crystals was measured by fixed funnel method.

Mechanical Property

Mechanical Properties[8-10] like tensile strength of microparticles (prepared by spray drying and spray chilling) were determined by compressing 500 mg of microparticals using hydraulic press at different ton/cm^2 for 1 min. The compacts stored in desiccator for overnight to allow elastic recovery. The thickness and diameter were measured for each compact. The hardness of each compact was then measured using Pfizer hardness tester. The tensile strength (σ) of the compact (ton/cm^2) was calculated using following equation.

$$\sigma = 2F/\pi Dt$$

Where, F, D and t are hardness (ton), compact diameter (cm) and thickness (cm), respectively.

Solubility studies

The solubility[12] of mefenamic acid microparticles (prepared by spray drying and spray chilling) in water was determined by taking excess quantity of microparticals in 50 ml to screw- capped glass vials filled with water. The vials were shaken for two hours on mechanical shaker. The solution was filtered through Whatmann filter paper No.1 and drug concentration was determined at 332 nm.

Dissolution studies of microparticals

The dissolution[7] of mefenamic acid pure sample, microparticles (prepared by spray drying and spray chilling) and recrystallized sample was determined by using USP dissolution apparatus XXIV-Type II (Electro Lab, Mumbai). Dissolution medium was 900 ml 7.4 Phosphate buffer. The amount of dissolved drug was determined using UV spectrophotometric method (UV 1601 A Shimadzu, Japan) at 332 nm.

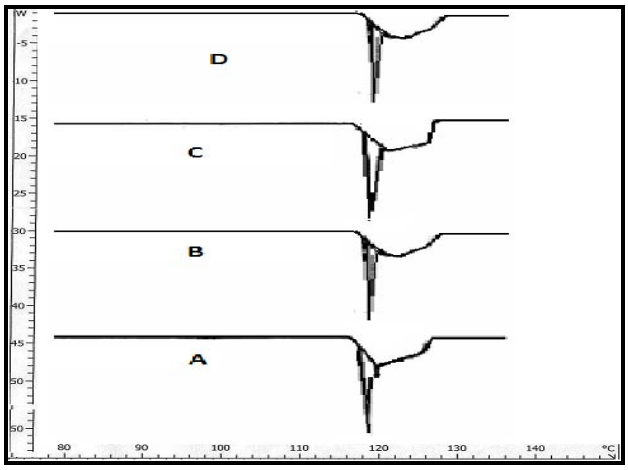
RESULTS AND DISCUSSION

The solvents chosen for the spray drying were Isopropyl alcohol (IPA) and water. These both the solvent were miscible in any proportion with each other.

The spray dried formulations collected and powders were free-flowing and white and in case of spray chilled particle was green in color. The percentage yield of spray dried mefenamic acid was found to be 58%.this small yield can be increase by adding of solid substance or in large scale production as it was small scale preparation. Drug content for the spray dried formulation was found to be 98±0.013. The percentage yield for spray chilled mefenamic acid particles was found to be 78%. Such yields are higher compared to spray dried products. Drug content for spray chilled mefenamic acid particle was found to be 96±0.012.

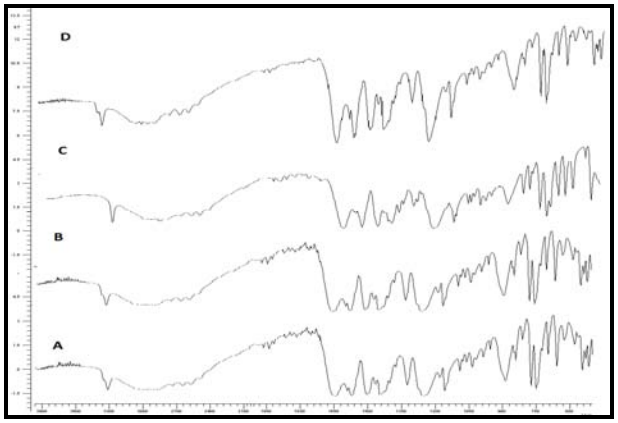
The DSC thermogram (fig. 1) shows a sharp endothermic peak for all the mefenamic acid. This one step melt might be due to only one crystal form (Triclinic) of the mefenamic acid formed during the crystallization process, thus indicating that mefenamic acid did not undergo any crystal modification. The temperature range of the endothermic peak of all the mefenamic acid crystals lies in the range of 230-240^0. Melting points show slight variation as the nature of the crystals might have been affected by the solvent. The mefenamic acid pure sample melted at 235.79°C with enthalpy of 173.5 J/g. The melting endotherm for spray dried micropartical of mefenamic acid was 232.43°C with decreased enthalpy of (129.34 J/g) indicating decreased crystallinity. The DSC thermograms of spray chilled mefenamic acid showed melting endotherm at the characteristic endothermic peak for the drug at 233.73°C with enthalpy of 156.37 J/g indicating decreased crystallinity but not compare to spray dried micropartical as spray dried microparical shows more decreased crystallinity then chilled particle. The decreased in crystallinity as follow: pure sample > recrystallized sample > chilled particle > spray dried micropartical.

Figure 1: (DSC) a-pure drug, b-recrystalized drug, c-chilled drug, d-spray dried



Infrared spectra of mefenamic acid commercial, recrystallized, spray chilled particle and spray dried microparticle showed characteristic peaks at 1255 cm^{-1} (-OH group bending and vibrations of COOH), 1647 cm^{-1} (N-H stretching vibration), 1572 cm^{-1} (C=O stretching), 1504 cm^{-1} (Aromatic C-H plane deformation), 1163 cm^{-1} (Aromatic-O-CH_3) and 757(Aromatic C-C vibration for ortho substitution). Spectrum of spray chilled particle of mefenamic acid was slightly different from pure sample in the region of wave number between 3350 and 3300 cm^{-1}. This may be suggests that the spray chilled particle of mefenamic acid prepared by heating the drug sample has a different crystalline form than its crystalline form in pure sample and in spray dried microparticle. It could be because of the degradation of drug or variations in the resonance structure, rotation of a part of a molecule or certain bonds. Alteration could be due to minor distortion of bond angles (Figure-2).

Figure 2: (FT-IR) a-pure drug, b-recrystalized drug, c-chilled drug, d-spray dried



All the samples showed similar peak positions (2θ) in X-ray diffraction, formation of different polymorphs of mefenamic acid was ruled out. However relative intensities of XRD peaks were modified (fig. 3). This could be attributed to the markedly different crystal habits of the samples (Table 1). Therefore the relative abundance of the planes exposed to the X-ray source would have been altered, producing the variations in the relative intensities of the peak or may be due to differences in particle sizes.

Figure 3: (XRD) a-pure drug, b-recrystalized drug, c-chilled drug, d-spray dried

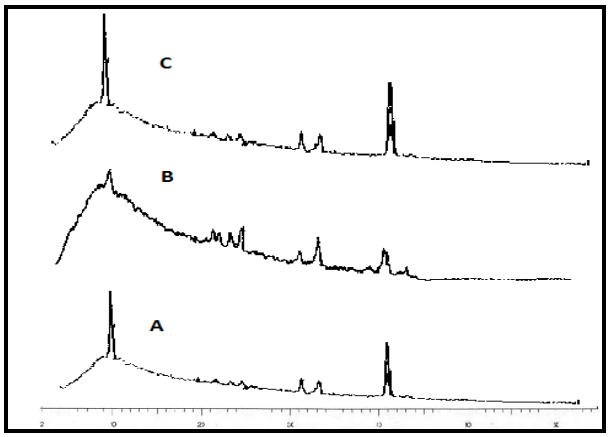


Table 1: Different cell parameters obtained for mefenamic acid crystals from XRD data.

	a	b	c	α	β	γ	Unit cell volume
Pure sample	15.68	14.17	12.73	88.21	83.43	90.01	2439.47
Recrystallized Sample	14.73	9.15	10.43	89.10	89.52	88.77	2410.09
Chilled spray dried particle	12.62	9.78	10.96	90.26	90.37	89.99	2179.09
Spherical crystals	7.73	10.65	12.52	95.24	87.29	75.83	653.48

a, b, c – three sides of cell expressed in A^0.

α, β, γ - three angles of the cell expressed in degrees

Figure 4: (SEM) A) p.s-pure drug, B) recrystallized sample C) C.S-chilled spray partical samlpe, D) SD.S-spray dried sample

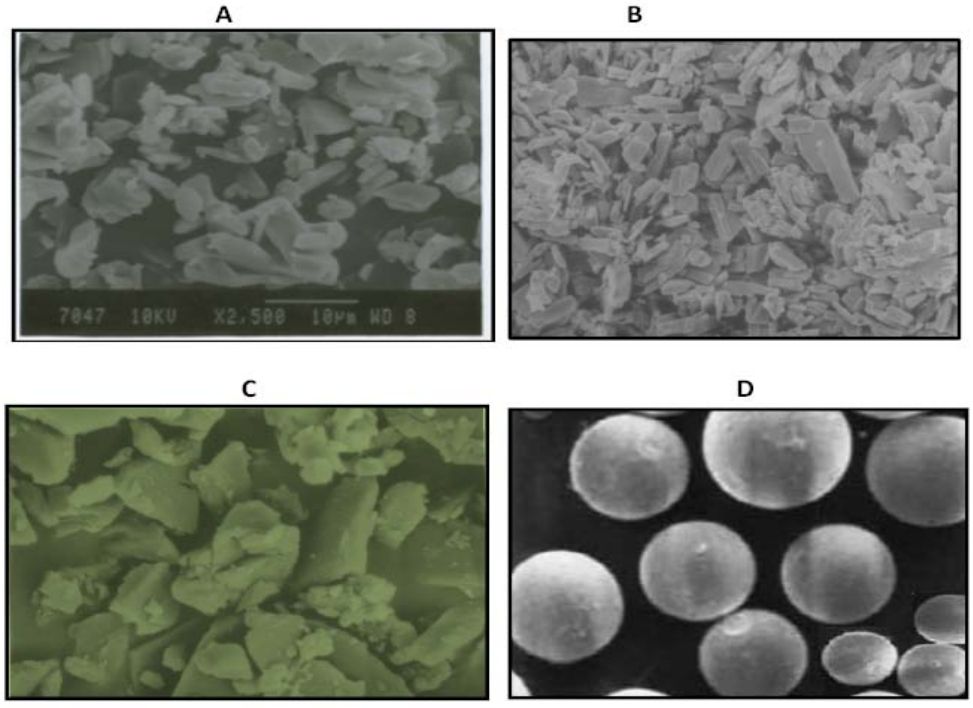


Table 2: micrometrics property of mefenamic acid of different samples

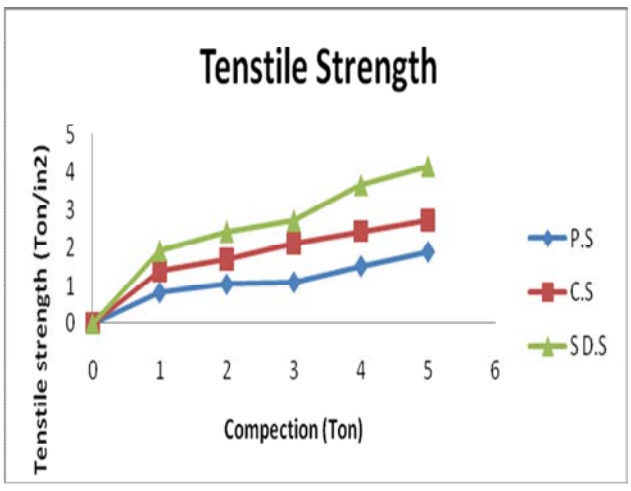
Properties	Pure sample	Recrystallized Sample	Chilled spray dried particle	Spray dried particle
Particle size (μm)	4-8	5-13	42-68	6-11
Flow rate (gm/Sec)	No flow	No flow	1.32	2.84
Angle of repose	38.50	34.13	30.32	27.24
Tapped density (gm/ml)	0.8179±0.013	0.5684±0.043	0.5252±0.052	0.2063±0.05
Bulk density(gm/ml)	0.6166±0.012	0.4268±0.06	0.3642±0.002	0.1916±0.004
Carr's index	27.17	25.18	23.78	11.19
Porosity (%)	0.3710	0.6851	0.6917	0.9086

Particle of pure sample are of the smallest size (4-8 μm) and they have irregular shapes. Recrystallization produced crystals with intermediate size (5-13 μm). The particle formed by spray chilled particle are large size compare to pure and irregular shape, with size of (42-68) μm. Microparticals formed by spray drying technique and the resultant Micropartical had a smooth surface (fig's. 4). Microparticals obtained were spherical in shape with small size (6-11) μm.

The Micrometrics properties of Pure Sample, Recrystallized Sample, Chilled spray dried particle and spray dried micropartical of mefenamic acid shown below: (Table 2).

Spray dried microparticals exhibited superior compressibility characteristics compared to pure sample and chilled spray dried particle (fig. 5). It could be due to the fact that during the process of compression fresh surfaces are formed by fracturing crystals. Surface freshly prepared by fracture enhanced the plastic inter particle bonding, resulting in a lower compression force required for compressing the agglomerates under plastic deformation compared to that of single crystal. Tensile strength of the mefenamic acid exhibited compressibility as follow: pure sample > chilled particle > spray dried micropartical.

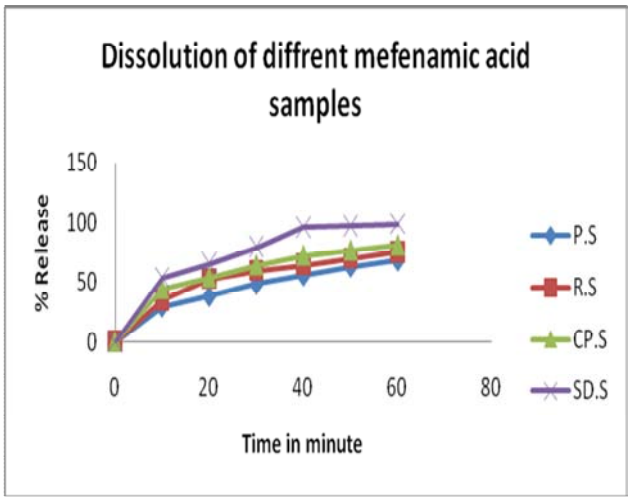
Figure 5: Tensile strength of P.S-pure drug, C.S-chilled spray particle sample, SD.S-spray dried sample



The solubility of mefenamic acid spray dried microparticles in water was found to be (0.0526) which was higher greater than spray chilled particle (0.0197), recrystallized sample (0.0094) and pure sample (0.0083). According to above result spray drying technique has good ability to increasing the solubility of poorly water soluble drug then other technique.

The dissolution profiles of mefenamic acid (fig. 6) exhibited improved dissolution behaviour for spray dried micropartical than spray chilled particle, recrystallized sample and pure sample. The reason for this faster dissolution could be linked to the better wettability of the micropartical. The amount of drug dissolved in 60 min greatly varied for spray dried micropartical. The dissolution of spray chilled particle was increases then recrystallized sample and pure sample but not much as in case of spray dried microparticles. This could be due to the degradation of drug due to heating with less solubility characteristics compared to the spray dried micropartical. Therefore, based on these results together with the assumption of formation of melt-solidified bonds could explain the low dissolution from particles prepared by spray chilling technique.

Figure 6: Shows Dissolution of: P.S-pure drug sample, R.S-recrystallized sample, CP.S-chilled spray dried particle sample, SD.S-spray dried sample



CONCLUSION

Spray dried micropartical of mefenamic acid were prepared by spray drying technique and chilled spray dried particle to improve the dissolution rate. Spray dried micropartical and chilled particle exhibited decreased crystallinity and improved micromeritic properties. DSC and XRD studies showed that there is no change in the crystal structure of mefenamic acid during the spray drying process i.e., polymorphism has not occurred. The dissolution of the spray dried micropartical was improved compared with spray chilled particle, Recrystallized sample and pure sample. spray chilled particle of mefenamic acid reduced the drug release as well as compared to the spray dried micro particle this could be due to the degradation of drug by heating or it could be variations in the resonance structure, rotation of a part of a molecule or certain bonds. Alteration could be due to minor distortion of bond angles. Hence spray chilling is not a suitable technique to improve dissolution of mefenamic acid as compare to spray drying technique.

Hence this spray drying technique can be used for formulation of tablets of mefenamic acid by direct compression with directly compressible tablet excipients.

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